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C2C CAA CBC CKH CKR CKS CLL CLM CTY CUH CWC C1343 C136X C1473 C21X C213 C247 C25Y C250 C251 C253 C256 C28X C280 C281 C29X C29Y C30Y C305 C31Y C313 C32Y C320 C321 C323 C339 C34Y C342 C35X C351 C352 C355 C36Y C364 C365 C366 C368 C386 C387 C388 C40Y C401 C43X C440 C50Y C509 C604 C62X C620 C623 C625 C628 C635 C644 C65X C670 C672 C675 C678 C760 C80Y C802
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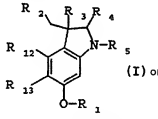
(71) Applicant(s)
Pharmacia & Upjohn S.p.A.
(Incorporated in Italy)
Via Robert Koch 1.2, 20152 Milan, Italy

(72) Inventor(s)
Italo Beria
Paolo Cozzi
Pier Giovanni Baraldi
Giampiero Spalluto
Maria Cristina Geroni

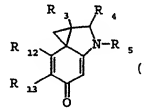
(74) Agent and/or Address for Service
J A Kemp & Co.
14 South Square, Gray's Inn, LONDON, WC1R 5LX, United Kingdom

(54) Abstract Title
Anti-tumour thieno-indole derivatives

(57) Thieno-indole derivatives of formula:



(I) or



(IA)

wherein the symbols are as defined in the specification, are novel compounds useful as anti-tumour agents.

Corresponding compounds (I) in which R_5 is an amino-protecting group and R_1 is a hydroxy-protecting group are novel intermediates.

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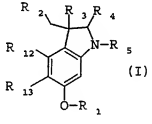
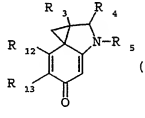
THIENO-INDOLE DERIVATIVES

The present invention relates to thieno-indole derivatives, to pharmaceutical salts thereof, to a process for their preparation, to novel intermediates useful for their synthesis, to pharmaceutical compositions comprising them and to their use as therapeutic agents, in particular as antitumor agents.

It is an object of the present invention to provide a compound which is a thieno-indole derivative of formula (I) or (IA)



(I)



(IA)

wherein

R_1 is hydrogen; C_1-C_4 alkyl; $-COR_6$ wherein R_6 is C_1-C_4 alkyl unsubstituted or substituted by phenyl which, in its turn, is unsubstituted or substituted by 1 to 3 substituents independently chosen from C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen and CF_3; or $-CONHR_6$ wherein R_6 is as defined above;

R_2 is halogen;

R_3 and R_4 are, each independently, hydrogen or C_1-C_4 alkyl;

R_5 is hydrogen or a substituent selected from:

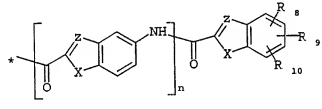
a) COR_7 in which R_7 is i) C_1-C_4 alkoxy or ii) a saturated or unsaturated, straight or branched C_1-C_{18} aliphatic hydrocarbon chain unsubstituted or substituted by one or more substituents independently chosen from hydroxy, C_1-C_4 alkoxy, cyano, $-C(NH)-NH_2$ and $-NR'R''$ in which R' and R'', being the same or different, are

hydrogen or C_1-C_4 alkyl, or iii) a saturated or unsaturated, straight or branched C_1-C_{12} aliphatic hydrocarbon chain ω-substituted by an aryl or heteroaryl group which, in its turn, is unsubstituted or substituted by 1 to 4 substituents independently chosen from halogen, hydroxy, C_1-C_4 alkoxy, cyano and $-C(NH)-NH_2$;

b) a saturated or unsaturated, straight or branched C_1-C_{18} aliphatic hydrocarbon chain substituted or unsubstituted by one or more substituents independently chosen from hydroxy, C_1-C_4 alkoxy, cyano, $-C(NH)-NH_2$ and $-NR'R''$ in which R' and R", being the same or different, are hydrogen or C_1-C_4 alkyl;

c) a saturated or unsaturated, straight or branched C_1-C_{12} aliphatic hydrocarbon chain ω-substituted by an aryl or heteroaryl group which, in its turn, is unsubstituted or substituted by 1 to 4 substituents independently chosen from halogen, hydroxy, C_1-C_4 alkoxy, cyano and $-C(NH)-NH_2$; and

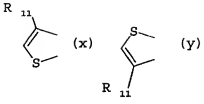
d) a group of formula (III)



(III)

wherein n is 0, 1 or 2; each of Z group is independently -CH= or -N=; each of X group is independently -O-, -S- or -NR- wherein R is hydrogen or C_1-C_4 alkyl; and each of R_8, R_9 and R_{10} is independently hydrogen, halogen, hydroxy, C_1-C_4 alkoxy, cyano, $-C(NH)-NH_2$ or $-NR'R''$ in which R' and R" are as defined above;

R_{12} and R_{13} taken together form a group (x) or (y):



in which R_{11} is hydrogen or C_1-C_4 alkyl;
or a pharmaceutically acceptable salt thereof.

The term C_1-C_4 alkyl includes methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl and tert-butyl.

The term halogen includes chlorine, bromine, fluorine and iodine.

The term C_1-C_4 alkoxy includes methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, sec-butoxy and tert-butoxy.

Preferred compounds of the invention are compounds wherein, in formula (I) or (IA):

R_1 is hydrogen, $-COR_6$ or $-CONHR_6$ wherein R_6 is as defined above;

R_2 is as defined above;

R_3 and R_4 are both hydrogen;

R_5 is COR_7 in which R_7 is C_1-C_4 alkoxy, or a group of formula (III) as defined above;

R_{12} and R_{13} taken together form a group (x) or (y) as defined above, in which R_{11} is C_1-C_4 alkyl;

and the pharmaceutically acceptable salts thereof.

More preferred compounds according to the invention are compounds wherein, in formula (I) or (IA):

R_1 is hydrogen, $-COR_6$ or $-CONHR_6$ wherein R_6 is as defined above;

R_2 is as defined above;

R_3 and R_4 are both hydrogen;

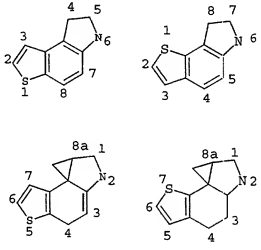
R_5 is a group of formula (III) as defined above in which Z is $-CH=$, X is independently $-O-$ or $-NH-$ and each of R_8, R_9

and R_{10} is independently hydrogen, halcgen, hydroxy, C_1-C_4 alkoxy, cyano, -C(NH)-NH_2 or -NR'R" in which R' and R" are as defined above;

R_{12} and R_{13} taken together form a group (x) or (y) as defined above, in which R_{11} is C_1-C_4 alkyl;

and the pharmaceutically acceptable salts thereof.

For clarity sake, the following numbering is used herein for the compounds of the invention



The invention includes also all the possible isomers, typically the stereoisomers and their mixtures, the metabolites and the metabolic precursors or bio-precursors (otherwise known as pro-drugs) of compounds of formula (I) and (IA).

Examples of specific compounds under this invention are the following:

1) (±)7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one;

2) (±)6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one;

3) (±)2-(tert-butyloxycarbonyl)-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one;

4) (±)2-(tert-butyloxycarbonyl)-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one;

5) (±)2-(5-amino-1H-indol-2-ylcarbonyl)-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one;
6) (±)2-(5-amino-1H-indol-2-ylcarbonyl)-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one;
7) (±)2-(5-amino-1H-benzofuran-2-ylcarbonyl)-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one;
8) (±)2-(5-amino-1H-benzofuran-2-ylcarbonyl)-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one;
9) (±)2-(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one;
10) (±)2-(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one;
11) (±)2-[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one;
12) (±)2-[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one;
13) (±)2-[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one;
14) (±)2-[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one;
15) (±)2-[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one hydrochloride;
16) (±)2-[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one hydrochloride;

17) (±)2-[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one hydrochloride;

18) (±)2-[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one hydrochloride;

19) (±)2-[5-[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one;

20) (±)2-[5-[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one;

21) (±)2-[5-[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one;

22) (±)2-[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one;

23) (±)2-[5-[[5-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one;

24) (±)2-[5-[[5-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one;

25) (±)2-[5-[[5-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one;

26) (±)2-[5-[[5-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one;

(27) (±)3-methyl-4-(chloromethyl)-8-hydroxy-4,5-dihydro-thieno[3,2-e]-indole;
28) (±)2-methyl-4-hydroxy-8-(chloromethyl)-7,8-dihydro-thieno[2,3-e]-indole;
29) (±)3-methyl-4-(chloromethyl)-6-(tert-butyloxycarbonyl)-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole;
30) (±)2-methyl-4-hydroxy 6-(tert-butyloxycarbonyl) 8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole;
31) (±)3-methyl-4-(chloromethyl)-6-(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole;
32) (±)2-methyl-4-hydroxy-6-(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole;
33) (±)3-methyl-4-(chloromethyl)-6-[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole;
34) (±)2-methyl-4-hydroxy-6-[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole;
35) (±)3-methyl-4-(chloromethyl)-6-[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole;
36) (±)2-methyl-4-hydroxy-6-[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole;
37) (±)3-methyl-4-(chloromethyl)-6-(5-amino-1H-indol-2-ylcarbonyl)-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole;
38) (±)2-methyl-4-hydroxy-6-(5-amino-1H-indol-2-ylcarbonyl)-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole;
39) (±)3-methyl-4-(chloromethyl)-6-(5-amino-1H-benzofuran-2-ylcarbonyl)-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole;
40) (±)2-methyl-4-hydroxy-6-(5-amino-1H-benzofuran-2-ylcarbonyl)-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole;

41) (±)3-methyl-4-(chloromethyl)-6-[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole;

42) (±)2-methyl-4-hydroxy-6-[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole;

43) (±)3-methyl-4-(chloromethyl)-6-[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole;

44) (±)2-methyl-4-hydroxy-6-[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole;

45) (±)3-methyl-4-(chloromethyl)-6-[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole;

46) (±)2-methyl-4-hydroxy-6-[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole;

47) (±)3-methyl-4-(chloromethyl)-6-[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole;

48) (±)2-methyl-4-hydroxy-6-[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole;

49) (±)3-methyl-4-(chloromethyl)-6-[5-[[5-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amiro]-1H-indol-2-ylcarbonyl]-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole;

50) (±)2-methyl-4-hydroxy-6-[5-[[5-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole;

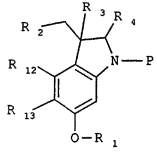
51) (±)3-methyl-4-(chloromethyl)-6-[5-[[5-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole;

52) (±)2-methyl-4-hydroxy-6-[5-[[5-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole;

and, if the case, the pharmaceutically acceptable salts thereof.

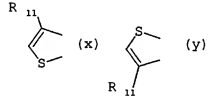
The compounds of formula (I) and (Ia), according to the present invention, and the salt thereof can be obtained by a process comprising:

A) removing the protecting group in a compound of formula (IV)



(IV)

wherein P is an amino protecting group; R_1 is hydrogen; R_2 is halogen; R_3 and R_4 are, each independently, hydrogen or C_1-C_4 alkyl; R_{12} and R_{13} taken together form a group (x) or (y):



in which R_{11} is hydrogen or C_1-C_4 alkyl; under acidic conditions, thus obtaining a compound of formula (I) in which R_1 and R_5 are hydrogen and R_2, R_3, R_4, R_{12} and R_{13} are as defined above; or

B) reacting a compound of formula (I), wherein R_5 is hydrogen, R_1, R_2, R_3, R_4, R_{12} and R_{13} are as defined above, with a compound of formula (V)

$$R'_5\text{-}W \qquad (V)$$

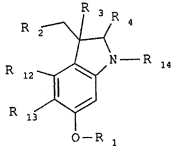
wherein R'_5 is as R_5 defined above under a) or d) and W is OH or a good leaving group, thus obtaining a compound of formula (I) wherein R_5 is as defined above under a) or d), respectively; or

C) reacting a compound of formula (I), wherein R_5 is hydrogen and R_1, R_2, R_3, R_4, R_{12} and R_{13} are as defined above, with a compound of formula (VI)

$$R''_5\text{-}W' \qquad (VI)$$

wherein R''_5 is as R_5 defined above under b) or c) and W' is halogen, thus obtaining a compound of formula (I), wherein R_5 is as defined above under b) or c), respectively; or

D) reacting a compound of formula (VII)



(VII)

wherein R_1 is hydrogen, R_{14} is either an amino protecting group or as R_5 as defined above under a) to d) and R_2, R_3, R_4, R_{12} and R_{13} are as defined above, with a compound of formula (VIII)

$$W'\text{-}C_1\text{-}C_4 \text{ alkyl} \qquad (VIII)$$

wherein W' is halogen, thus obtaining after removal of the amino protecting group, if present, a compound of

formula (I), wherein R_1 is C_1-C_4 alkyl, R_5 is hydrogen or as defined above under a) to d) and R_2, R_3, R_4, R_{12} and R_{13} are as defined above; or

E) reacting a compound of formula (VII) as defined above with a compound of formula (IX)

$$W\text{-}COR_6 \qquad (IX)$$

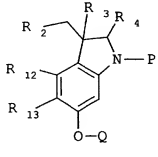
wherein W and R_6 are as defined above, thus obtaining after removal of the amino protecting group, if present, a compound of formula (I) wherein R_1 is $-COR_6$, R_5 is hydrogen or as defined above under a) to d) and R_2, R_3, R_4, R_{12} and R_{13} are as defined above; or

F) reacting a compound of formula (VII) as defined above with a compound of formula (X)

$$R_6\text{-}N{=}CO \qquad (X)$$

wherein R_6 is as defined above, thus obtaining after removal of the amino protecting group, if present, a compound of formula (I) wherein R_1 is $-CONR_6$, R_5 is hydrogen or as defined above under a) to d) and R_2, R_3, R_4, R_{12} and R_{13} are as defined above; or

G) removing the amino and hydroxy protecting groups in a compound of formula (XI)



(XI)

wherein Q is a hydroxy protecting group, P is an amino protecting group and R_2, R_3, R_4, R_{12} and R_{13} are as defined above, thus obtaining a compound of formula (I) wherein R_1 and R_5 are hydrogen; or

H) removing the hydroxy protecting group in a compound of formula (XI) wherein P, being as defined above is -COO-tert-butyl and Q, R_3 and R_4, R_{12} and R_{13} are as defined above, thus obtaining a compound of formula (I) wherein R_1 is hydrogen and R_5, being a COR_7 group as defined above, is -COO-tert-butyl; or

I) reacting a compound of formula (I), in which R_1 is hydrogen and R_2, R_3, R_4, R_5, R_{12} and R_{13} are as defined above, with a basic agent, thus obtaining a compound of formula (IA);

and if desired, converting a compound of the invention into another compound of the invention, and/or, if desired, converting a compound of the invention into a salt thereof, and/or, if desired converting a salt of a compound of the invention into a free compound, and/or, if desired, separating a mixture of isomers of a compound of the invention into the single isomers.

Process-variants A) to I) according to this invention are analogy processes. For instance they can be performed as described herebelow.

In a compound (IV) P as amino protecting group is, for instance, an amino protecting group according to the peptidic chemistry. Preferably, it is a benzyloxycarbonyl or a C_1-C_4 alkoxycarbonyl group, in particular a tert-butoxycarbonyl group.

Removal of an amino protecting group in a compound of formula (IV) can be carried out using known methods, e.g. as described in J.Org.Chem. 43, 2285 (1978).

In a compound of formula (V) W as a leaving group is, for instance, a halogen atom preferably chlorine or an imidazolyl group.

The reaction of a compound of formula (I) with a compound of formula (V) can be carried out according to known methods. If necessary, the hydroxy group in a compound of formula (I) can be protected before the reaction takes place and then deprotected at the end of the reaction, according to known methods. Examples of hydroxy protecting groups are benzyl and tetrahydropyranyl.

The reaction between a compound of formula (I) and a compound of formula (V) wherein W is OH, is preferably carried out in a molar ratio ranging from about 1:1 to about 1:2, in an organic solvent such as, e.g. dimethylsulfoxide, dioxane, or preferably dimethylformamide in presence of a condensing agent such as, e.g. N,N'-dicyclohexylcarbodiimide or preferably 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride.

The reaction temperature may vary from about -10° to about 60°C and the reaction time from about 1 hour to about 24 hours.

The reaction between a compound of formula (I) and a compound of formula (V) wherein W is a leaving group as defined above, may be carried out in a molar ratio ranging from about 1:1 to about 1:2, in an organic solvent such as, e.g. dimethylformamide, dioxane, or an aqueous mixture thereof, in the presence of an organic base, e.g. sodium bicarbonate, at a temperature from about 0°C to about 100°C and for a time varying from about 2 hours to about 48 hours.

In a compound of formula (VI), W' as halogen atom is, e.g. chlorine or bromine. When reacting a compound of formula (I) with a compound of formula (VI), if necessary, the hydroxy group in the compound of formula (I) can be protected and then deprotected at the end of the reaction as described above.

The reaction of a compound of formula (I) with a compound of formula (VI) can be carried out, for instance, as

described in J. Am. Chem. Soc. 54, 1499 (1932); ibidem 3441; ibidem 4457; ibidem 82, 6163 (1960).

In a compound of formula (VII) R_{10} as amino protecting group can be, for instance, an amino protecting group known from the chemistry of peptides and, if desired, can be removed according to known methods at the end of any reaction according to process variants D), E) and F).

In a compound of formula (VIII) W' as halogen atom is, e.g. chlorine or bromine. The reaction of compound of formula (VII) with a compound of formula (VIII) can be carried out according to known methods; for instance, those described above as to the reaction of a compound of formula (I) with a compound of formula (VI).

In a compound of formula (IX) W as a leaving group is, for instance, one of the groups mentioned above as to a compound of formula (V). The reaction of a compound of formula (VII) with a compound of formula (IX) can be carried out by following the same procedures described above as to the reaction of a compound of formula (I) and a compound of formula (V).

The reaction of a compound of formula (VII) with a compound of formula (X) can be performed according to known methods, e.g. as reported in J.Org. Chem. 42, 1428 (1977); Synthesis 131 (1989); J. Chem. Soc. Perkin Trans. 2, 1029 (1985).

A hydroxy protecting group Q in a compound of formula (XI), according to process-variants G) and H), can be a hydroxy protecting group known from the chemistry of peptides, e.g. one of those mentioned above such as benzyl.

Similarly, an amino protecting group P in a compound of formula (XI), according to process G), can be one of those known from the chemistry of peptides; for instance, one of those mentioned above such as -COO-tert-butyl.

Selective removal of the hydroxy protecting group in a compound of formula (XI), according to process H), can be performed by using known methods as those reported in J. Org. Chem. 44, 3442 (1979); Synthesis 76 (1985).

The same methods can be used for removing the hydroxy protecting group in a compound of formula (XI), according to process G); removal of the amino protecting group in the same compound can be carried out using known methods as, e.g., those described in J. Org. Chem. 43, 2285 (1978).

A basic agent according to process variant I) can be either an inorganic base such as, e.g. an alkaline carbonate or bicarbonate salt, or an organic base such as, e.g. sodium hydride or triethylamine. The reaction can be carried out in an organic solvent such as, e.g., dioxane, dimethylformamide or tetrahydrofuran. The reaction time may vary from about 2 hours to about 48 hours and the reaction temperature from about 0°C to about 50°C.

The optional salification of a compound of formula (I) or (IA), as well as the conversion of a salt thereof into a free compound and the separation of a mixture of isomers of a compound of formula (I) or (IA) into the respective single isomers can be carried out according to known methods.

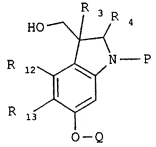
A compound of the invention, if desired, can be converted into another compound of the invention according to known methods. For instance, a compound of formula (IV) in which the amino protecting group P is tert-butoxycarbonyl can be regarded as a compound of formula (I) in which R_5 is $-COR_7$ in which R_7 is tert-butyloxy. Similarly, a compound of formula (VII) in which R_{10} is as R_5 defined under a) to d) can be regarded as a compound of formula (I) in which R_5 is as defined above under a) to d). Therefore, reactions involving a compound of formula (IV) or of formula (VII) can be regarded, according to particular values of the substituents, as a conversion of a compound of formula (I) into another compound of formula (I). Similarly, processes b) and c) are acylation and alkylation reactions, respectively, on a compound of formula (I), namely

conversions of a compound of formula (I) into another compound of formula (I).

The compounds of formula (IV) are either compounds of formula (I), as stated above, or can be obtained by removing the hydroxy protecting group in a compound of formula (XI) according to known methods.

The compounds of formula (VII) are either compounds of formula (I), as stated above, or can be obtained by removing the amino protecting group in a compound of formula (XI), according to known methods, and then acylating or alkylating the free amino group as per processes B) and C), respectively, in order to introduce the R_{10} substituent, followed by removal of the hydroxy protecting group by known methods.

According to a preferred embodiment of the invention, the compounds of formula (XI) may be prepared by halogenating a compound of formula (XII)



(XII)

wherein P, Q, R_3, R_4, R_{12} and R_{13} are as defined above, with a halogenating agent, such as, e.g. carbon tetrachloride or triphenylphosphine.

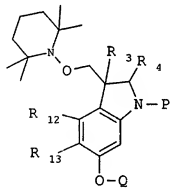
The reaction can be carried out using known methods, for example as those reported in J. Am. Chem .Soc. 111, 6461 (1989).

The compounds of formula (XI) are new compounds and are a further object of the present invention.

The compounds of formulae (V), (VI), (VIII), (IX) and (X) are either known compounds or can be obtained from known compounds according to known methods.

For instance the following compounds of formula (V) in which R'_5 is a group d) as defined above are known from the following literature:

1H-benzoimidazole-2-carboxylic acid [J.Chem.Soc. Perkin Trans. 1, 2871 (1982)]; 2-benzothiozolecarboxylic acid, ethyl ester [Tetr. Letters 23, 3357 (1982)]; 2-benzofuran carboxylic acid [Org.Synth.Coll. III, 209-211]; 5-amino-1H-indole-2-carboxylic acid [C.A. Reg. No. 71086-99-2]; 5-amino-1H-indole-2-carboxylic acid [J.Am.Chem.Soc. 80, 4621 (1958); 5-hydroxy-1H-indole-2-carboxylic acid [C.A. Reg. No. 21598-06-1]; 5-hydroxy-benzo[b]-thiophene-2-carboxylic acid, methylester [C.A. Reg. No. 82788-15-6].by reacting a compound of formula (XIII)



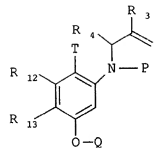
(XIII)

wherein R_3, R_4, R_{12}, R_{13}, P and Q are as defined above, with a suitable reducing agent.

The reaction can be carried out, for example, using an organic solvent such as, e.g., dioxane, tetrahydrofuran or preferably toluene, or a water mixture, in acidic condition, in the presence of a reducing agent such as, e.g. zinc powder.

The reaction temperature may vary from about 20°C to reflux and the reaction time from about 1 hour to about 24 hours.

A compound of formula (XIII) can be obtained by cyclizing a compound of formula (XIV)



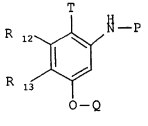
(XIV)

wherein R_3, R_4, R_{12}, R_{13} P and Q are as defined above and T is a halogen such as, e.g., chlorine, bromine, or preferably iodine.

The reaction can be carried out in an organic solvent such as, e.g., dioxane, tetrahydrofuran or preferably toluene, under argon with commercial tris(trimethylsilyl)silane and 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical.

The reaction temperature may vary from about 50°C to reflux and the reaction time from about 1 hour to about 5 hours.

A compound of formula (XIV) can be prepared from a compound of formula (XV)

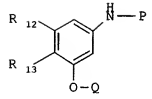


(XV)

wherein R_{12}, R_{13}, P, Q and T are as defined above, with the opportune allil bromide and sodium hydride, in an organic solvent such as, e.g. DMF.

The reaction temperature may vary from about -10°C to about 50°C and the reaction time from about 1 hour to about 48 hours.

A compound of formula (XV) can be prepared from a compound of formula (XVI)



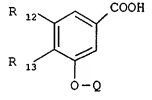
(XVI)

wherein R_{12}, R_{13}, P and Q are as defined above.

The reaction can be carried out in an organic solvent such as, e.g. THF, in presence of pTsOH-H_2O, iodosuccinimide and a catalitic amount of iodine.

The reaction temperature may vary from about -10°C to about 30°C and the reaction time from about 5 minutes to about 12 hours.

A compound of formula (XVI) can be prepared from a compound of formula (XVII)



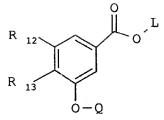
(XVII)

wherein R_{12}, R_{13} and Q are as defined above.

The reaction can be carried out in an organic solvent such as, e.g. an aliphatic C_1-C_4 alcohol, preferably tert-butanol, using from about 1 to about 1.5 eq. of diphenylphosphoryl azide, in presence of about 1.2 eq. of an organic base such as, e.g. triethylamine.

The reaction temperature may vary from about 0°C to about 150°C and the reaction time from about 5 hours to about 24 hours.

A compound of formula (XVII) can be prepared by hydrolysis of a compound of formula (XVIII)

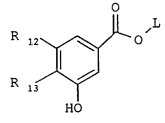


(XVIII)

wherein R_{12}, R_{13} and Q are as defined above and L is a C_1-C_4 alkyl group, such as methyl, propyl, isopropyl or, preferably, ethyl.

The reaction can be carried out by hydrolytic condition according to known procedure, using for instance NaOH, KOH or ,preferably, LiOH, in a mixture of water and organic solvent such as,e.g., dioxane, tetrahydrofuran, methanol, ethanol or acetonitrile, at room temperature and for a time from about 2 hours to about 24 hours.

A compound of formula (XVIII) can be prepared from a compound of formula (XIX)

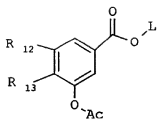


(XIX)

wherein R_{12}, R_{13} and L are as defined above.

The reaction can be carried out according to known procedure as those reported in Methods Carbohydr. Chem. II, 166 (1963), using benzyl bromide and K_2CO_3, in an organic solvent such as, e.g. dimethylformamide.

A compound of formula (XIX) can be prepared from a compound of formula (XX)



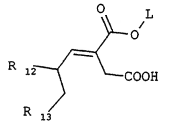
(XX)

wherein R_{12}, R_{13} and L are as defined above.

The reaction can be carried out in an organic solvent such as, e.g., methanol or preferably ethanol, in presence of sodium carbonate or potassium carbonate.

The reaction temperature may vary from about 70°C to about 90°C and the reaction time from about 12 hours to aout 24 hours.

A compound of formula (XX) can be prepared by cyclizing a compound of formula (XXI)

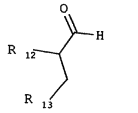


(XXI)

wherein R_{12}, R_{13} and L are as defined above.

The reaction can be carried out in an organic solvent such as, e.g., acetic anhydride, in presence of an excess of sodium acetate according to known procedure as those reported in J. Med. Chem. Vol. 31, 590 (1988).

A compound of formula (XXI) can be prepared from a compound of formula (XXII)



(XXII)

with diethysuccinate, using a known prccedure as reported in Helv. Chim.Acta 62, 90 (1979).

The reaction can be carried out in an organic solvent such as, e.g. tert-butanol, in presence of an organic base such as, e.g. potassium tert-butoxide.

The reaction temperature may vary from about 80°C to about 130°C and the reaction time from about 1 hour to about 12 hours.

The compounds of formula (XXII) are commercially available compounds or can be prepared using known methods, for example using the methods described in the European Patent Application EP 432817 A1.

When in the reactions involving the intermediate compounds of the present invention, free hydroxy and/or amino group need to be protected before the reaction take place and deprotected at the end of the reaction, such protections and deprotections can be carried out as known from the peptide chemistry, for instance as herein described.

The compounds of the invention have cytotoxic properties toward tumor cells.

The cytotoxicity of the compounds of the invention was evaluated, for instance, on murine L1210 leukemia cells, sensitive and resistant to Doxorubicin with the following procedure.

Cells were derived from <u>in vivo</u> tumors and established in cell culture.

Cells were used until the tenth passage and cytotoxicity was determined by counting surviving cells after 48 hours treatment.

By virtue of their valuable properties, the compounds of the present invention and the pharmaceutically acceptable salts thereof, can be useful in therapy as antineoplastic agents, e.g. to inhibit the growth of various tumors such as, for instance, carcinomas, e.g. mammary carcinoma, lung carcinoma, bladder carcinoma, colon carcinoma, ovary and endometrial tumors. Other neoplasias in which the compounds

of the invention can find application are, for instance, sarcomas, e.g. soft tissue and bone sarcomas, and the hematological malignancies such as, e.g., leukemias.

The compounds of the invention can therefore be used in a treatment to ameliorate a cancer pathology.

The compounds of the invention can be administered to mammals, including humans, by the usual routes, for example, parenterally, e.g. by intravenous injection or infusion, intramuscularly, subcutaneously, topically or orally.

The administration dosage of these drugs will vary depending upon the disease status of the individual.

The dosage regimen must therefore be tailored to the particular of the patient's conditions, response and associate treatments in a manner which is conventional for any therapy, and may need to be adjusted in response to changes in conditions and/or in light of other clinical conditions. A typical dosage range is from about 0.05 to about 20 mg pro dose, administered 1 to 4 times a day.

A further object of this invention is to provide a pharmaceutical composition comprising a compound of the invention, i.e. a compound of formula (I) or (IA) as defined above or a pharmaceutically acceptable salt thereof, as the active substance, in association with one or more pharmaceutically acceptable excipients and/or carriers. The pharmaceutical compositions are usually prepared following conventional methods and are administered in a pharmaceutically suitable form. For instance, solutions for intravenous injection or infusion may contain as carrier, for example, sterile water or preferably, they may be in the form of sterile aqueous isotonic saline solutions.

Suspensions or solutions for intramuscular injections may contain, together with the active compound a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol,

polyethylene (20) sorbitan mono-oleate, and if desired, a suitable amount of lidocaine hydrochloride.

In the form for topical application, e.g. creams, lotions or pastes for use in dermatological treatment, the active ingredient may be mixed with conventional oleaginous or emulsifying excipients.

The solid oral forms, e.g. tablets and capsules, may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch and potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethyl-cellulose, polyvinylpyrrolidone; disaggregating agents, e.g. a starch, alginic acid, alginates, sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, for instance, lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in a known manner, for example by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

Furthermore, according to the present invention there is provided a method of treating tumors in a mammal, including humans, in need of it, comprising administering to said mammal a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof.

The following examples illustrate but do not limit the invention.

The abbreviations DMF, MeOH, t-BuOK, t-BuOH, EtOAc, Et_2O, Tempo, THF and PMR stand, respectively, for dimethylformamide, methanol, potassium tertbutoxide, tertbuthanol ethyle acetate, diethyl ethere,

2,2,6,6-tetramethyl-1-piperidinyloxy free radical, tetrahydrofuran, and Proton Magnetic Resonance.

Example 1

(±)-3-methyl-4-(chloromethyl)-6-(tert-butyloxycarbonyl)-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole (comp. 29)

Step -1- The intermediate Ethyl *E*-4-[(4-methyl)-thiophen-3-yl]-3-ethoxycarbonyl-3-butenoate

A solution of t-BuOK (39.95 g, 0.356 mol) in t-BuOH (130 mL) was added to a mixture of 4-methylthiphen-4-carboxaldehyde (15 g, 0.12 mol), diethyl succinate (59.3 mL, 0.356 mol) and refluxed for 45 minutes. Then the same amounts of diethyl succinate and t-BuOK in t-BuOH were added and the mixture refluxed for other 45 minutes. The mixture was cooled, acidified with aqueous 20% HCl to pH 2 and extracted with EtOAc (3x50 mL). The organic layer was extracted with aqueous 5% Na_2CO_3 (5x50 mL). The alcaline solution was extracted with Et_2O (2x50 mL) and then acidified with aqueous 20% HCl to pH 2. This solution was extracted with EtOAc (4x40 mL) and the recombined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford the intermediate as an yellow oil which was used in the next step without further purifications.

By analogous procedure the following compound can be prepared:

Ethyl *E*-4-[(5-methyl)-thiophen-2-yl]-3-ethoxycarbonyl-3-butenoate

Step -2- The intermediate Ethyl 7-acetyloxy-3-methyl benzo[b]thiophen-5-carboxylate

A solution of crude intermediate 1 (30 g, 0.12 mol) in acetic anhydride (594 mL) and sodium acetate (9.75 g, 0.12 mol) was refluxed for 5 hours. The acetic anhydride was removed under reduced pressure and the residue was diluted

with aqueous 15% Na_2CO_3 (100 mL) and extracted with EtOAc (3x50 mL). The recombined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The dark-brown oil was purified by flash chromatography (Et_2O-light petroleum 1.5-8.5) to give the desired Intermediate as a pale yellow solid (yield 55%).

m.p. (Et_2O-light petroleum) 89-90 °C

IR (KBR) cm^{-1}: 1775, 1740, 1300, 1250, 1775, 1740, 1300, 1250

^1H NMR ($CDCl_3$) δ: 1.42 (t, 3H, J=4Hz); 2.41 (s, 3H); 2.47 (s, 3H); 4.41 (q, 2H, J=4Hz); 7.12 (s, 1H); 7.28 (s, 1H); 8.32 (s,1H).

By analogous procedure the following compound can be prepared:

Ethyl 4-acetyloxy-2-methylbenzo[b]thiophen-6-carboxylate

m.p. (Et_2O-light petroleum) 82-84 °C

IR (KBr) cm^{-1}: 1775, 1740, 1300, 1250

^1H NMR ($CDCl_3$) δ: 1.40 (t, 3H, J=8Hz); 2.42 (s, 3H); 4.41 (q, 2H, J=8Hz); 6.92 (s, 1H); 7.7 (s, 1H); 8.36 (s, 1H).

Step-3- The intermediate Ethyl 3-methyl-7-hydroxy-benzo[b]thiophen-5-carboxylate

A solution of intermediate 3 (4 g, 15.26 mmol) in dry ethanol (20 mL) and anhydrous potassium carbonate (2.3 g, 16.78 mmol) was refluxed for 18 hours. The ethanol was removed under reduced pressure, the residue dissolved in water (20 mL) and the resulting solution extracted with EtOAc (3x20 mL). The recombined organic layers were dried (Na_2SO_4) and concentrated to afford the crude product that after purification by flash chromatography (Et_2O-light petroleum 3:7) furnished the intermediate as a pale yellow solid (yield 95%).

m.p. (Et_2O-light petroleum) 150-152°C

IR (KBr) cm^{-1}: 3480, 1710, 1600, 1550, 1450

^1H NMR ($CDCl_3$) δ: 1.43 (t, 3H, J=7Hz); 2.47 (s, 3H); 4.42 (q, 2H, J=7Hz); 6.82 (s, 1H); 7.13 (s, 1H); 7.62 (s, 1H); 8.03 (s,1H).

By analogous procedure the following compound can be prepared:

Ethyl 2-methyl-4-hydroxy-benzo[b]thiophen-6-carboxylate

m.p..(Et_2O-light petroleum) 132-135 °C

IR (KBr) cm^{-1}: 3480, 1710, 1600, 1550, 1450

^1H NMR ($CDCl_3$) δ: 1.41 (t, 3H, J=8Hz); 2.61 (s, 3H); 4.40 (q, 2H, J=8Hz); 6.2 (s, 1H); 7.18 (s, 1H); 7.5 (s, 1H); 8.06 (s, 1H).

Step -4- The intermediate Ethyl 7-benzyloxy-3-methylbenzo[b]thiophen-5-carboxylate

A solution of the intermediate 3 (2.8 g, 12.72 mmol) in dry DMF (40 mL), under argon was treated with anhydrous potassium carbonate (2.45 g, 17.8 mmol), benzyl bromide (1.78 mL, 15.26 mmol) and stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure. The crude residue after flash chromatography (Et_2O-light petroleum 2:8) afforded the desired compound as a white solid (yield 98%).

m.p. (Et_2O-light petroleum) 150-152 °C

IR (KBr) cm^{-1}: 1710, 1560, 1550, 1450

^1H NMR ($CDCl_3$) δ: 1.43 (t, 3H, J=7Hz); 2.47 (s, 3H); 4.42 (q, 2H, J=7Hz); 5.3 (s, 2H); 5.3 (s, 2H); 7.12 (s, 1H); 7.16 (s, 1H); 7.37-7.53 (m, 5H); 8.08 (s,1H).

By analogous procedure the following compound can be prepared:

Ethyl 4-benzyloxy-2-methylbenzo[b]thiophen-6-carboxylate

m.p. (Et_2O-light petroleum) 90-92 °C

IR (KBr) cm^{-1}: 1710, 1560, 1550, 1450

^1H NMR ($CDCl_3$) δ: 1.35 (t, 3H, J=8Hz); 2.52 (s, 3H); 4.35 (q, 2H, J=8Hz); 5.16 (s, 2H); 7.17(s, 1H); 7.18-746 (m, 6H); 8.04 (s, 1H).

Step -5- The intermediate 7-Benzyloxy-3-methylbenzo[b]thiophen-5-carboxylic acid

To a solution of the intermediate 4 (3.8 g, 12.25 mmol) in THF/MeOH/H_2O in the ratio 4:1:1 (83 mL),lithium hydroxide (1.53 g, 36.75 mmol) was added. The mixture was stirred at room temperature for 18 hours. After this time, water was added (20 mL) and the resulting solution was acidified to pH 2 with aqueous 10 % HCl. The white precipitate was collected and crystallized (Et_2O-ligth petroleum) to afford the desired intermediate as a pale yellow solid (yield 98%).

m.p. (water) 187-189°C

IR (KBR) cm^{-1}: 3450, 1710, 1560, 1550, 1450

^1H NMR ($CDCl_3$) δ: 2.5 (s, 3H); 5.35 (s, 2H); 7.16 (s, 1H); 7.38-7.57 (m, 6H); 8.19 (s,1H); 13.01 (bs, 1H).

By analogous procedure the following compound can be prepared:

4-Benzyloxy-2-methylbenzo[b]thiophen-6-carboxylic acid

m.p. (water) 173-175 °C (dec.)

IR (KBr) cm^{-1}: 3500-3100, 1700, 1550

^1H NMR ($CDCl_3$) δ: 2.56 (s, 3H); 5.26 (s, 2H); 7.20 (s, 1H); 7.40-7.55 (m, 6H); 8.05 (s, 1H); 13.1 (bs, 1H).

Step -6- The intermediate 7-Benzyloxy-3-methyl-5-[N-(t-butoxycarbonyl)]aminobenzo[b]thiophene

A solution of intermediate 5 (2 g, 7.09 mmol) in dry t-BuOH (136 mL) was treated sequentially with diphenylphosphoryl azide (DPPA, 1.83 mL, 8.5 mmol), Et_3N (1.21 mL, 8.5 mmol).

The mixture was stirred at reflux for 18 hours, cooled and concentrated in vacuo. Flash chromatography (Et_2O-light petroleum 1:1) afforded the desired intermediate as a white solid (yield 83%).

m.p. (Et_2O-light petroleum) 172-173°C

IR (KBr) cm^{-1}: 3350, 1710, 1640, 1600, 1550, 1430

^1H NMR ($CDCl_3$) δ: 1.53 (s, 9H); 2.38 (s, 3H); 5.25 (s, 2H); 6.59 (s, 1H); 7.02-7.05 (m, 2H); 7.32-7.58 (m, 6H).

By analogous procedure the following compound can be prepared:

4-Benzyloxy-2-methyl-6-[N-(t-butoxycarbonyl)]amino benzo[b] thiophene

m.p. (Et_2O-light petroleum) 120-122 °C

IR (KBr) cm^{-1}: 3350, 1710, 1640, 1600, 1550, 1430

^1H NMR ($CDCl_3$) δ: 1.53 (s, 9H); 2.52 (s, 3H); 5.15 (s, 2H); 6.5 (s, 1H); 6.85 (s, 1H); 7.1 (s, 1H); 7.30-7.52 (m, 6H).

Step -7- The intermediate 7-Benzyloxy-3-methyl-5-[N-(t-butoxycarbonyl)]amino-4-Iodo benzo[b]thiophene

A solution of the intermediate 5 (1.03 g, 2.917 mmol), in dry THF (40 ml), under argon was cooled to 0 °C, and 30 mg of $pTsOH-H_2O$ in 1 mL of THF was added. After 5 minutes at 0 °C, N-Iodosuccinimmide (780 mg, 3.5 mmol) in THF (10 mL) and a catalytic amount of Iodine (5 mg) were added. Upon complete reaction (*ca.* 2h at room temperature, TLC: Et_2O-light petroleum 2 : 8), 10 mL of saturated aqueous $NaHCO_3$ and 50 mL of Et_2O were added. Organic layer was separated and the aqueous layer was extracted with Et_2O (3x15mL). The organic layers were recombined, washed with saturated aqueous $NaHCO_3$ (1x15 mL), 5% aqueous $Na_2S_2O_3$ (2x20 mL), dried and concentrated at reduced pressure to afford after crystallization (light petroleum) the desired intermediate as a pale yellow solid (yield 98%).

m.p. (Et_2O-light petroleum) 109-110 °C

IR (KBr) cm^{-1}: 3450, 1740, 1630, 1450, 1390

^1H NMR ($CDCl_3$) δ: 1.58 (s, 9H); 2.75 (s, 3H); 5.3 (s, 2H); 7.18 (s, 1H); 7.3-7.58 (m, 6H); 7.8 (s, 1H).

By analogous procedure the following compound can be prepared:

4-Benzyloxy-2-methyl-6-[N-(t-butoxycarbonyl)]amino-5-Iodobenzo[b]thiophene

m.p. (Et_2O-light petroleum) 127-129 °C

IR (KBr) cm^{-1}: 3150, 1710, 1650, 1450

^1H NMR ($CDCl_3$) δ: 1.58 (s, 9H); 2.55 (s, 3H); 5.22 (s, 2H); 6.86 (s, 1H); 7.39-7.54 (m, 6H); 7.78 (s, 1H).

Step-8- The intermediate 7-Benzyloxy-3-methyl-5-[N-(t-butoxycarbonyl)-4-Iodo-N-(2-propenyl)]amino benzo[b]thiophene

A solution of intermediate 6 (1.26 g, 2.91 mmol) in DMF (50 mL) cooled to 0 °C was treated with NaH (140 mg, 60% inoil, 3.49 mmol) in several portions over 10 minutes. After 45 minutes, allyl bromide (0.67 mL,7.99 mmol), was added and the reaction mixture was allowed to warm to 25 °C and stirred for 3 h (TLC: Et_2O-light petroleum 3 : 7). The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (15 ml), and the aqueous layer was extracted with EtOAc (3x20 mL). The organic layers were recombined, washed with water (2x10 mL) and saturated aqueous NaCl (2x15 mL), dried, filtered and concentrated at reduced pressure. Flash chromatography (Et_2O-light petroleum 3 : 7), afford the desired intermediate as a thick oil (yield 98%).

1R (film) cm^{-1}: 1710, 1600, 1550, 1380

^1H NMR ($CDCl_3$) δ: 1.31 (s, 6H); 1.55-1.62 (m, 3H); 2.74 (s, 3H); 3.5-3.15 (m, 1H); 4.4-4.46 (m, 1H); 4.9-5.29 (m, 4H); 5.73-5.99 (m, 1H); 6.53-6.75 (m, 1H); 7.19-7.45 (m, 6H).

By analogous procedure the following compound can be prepared:

4-Benzyloxy-2-methyl-6-[N-(t-butoxycarbonyl)-5-Iodo-N-(2-propenyl)]amino benzo[b] thiophene

m.p. (Et_2O-light petroleum) 140-141°C

IR (KBr) cm^{-1}: 1710, 1600, 1550, 1380

^1H NMR ($CDCl_3$) δ: 1.31 (s, 6H); 1.54 (s, 3H); 2.56 (m, 3H); 3.74-3.85 (m, 1H); 4.38-4.49 (m, 1H); 4.94-5.22 (m, 4H); 5.78-5.99 (m, 1H); 6.53-6.65 (m, 1H); 7.32-742 (m, 6H).

Step -9- The intermediate (±)-8-Benzyloxy-3-methyl-6-(tert-butyloxycarbonyl)-4-[(2',2',6',6'-tetramethylpiperidinyl-N-oxy)methyl]-4,5-dihydro-thieno[3,2-e]indole

A solution of intermediate 7 (1.25 g, 2.63 mmol) and Tempo (1.23 g, 7.89 mmol) in freshly distilled toluene (90 mL) under argon, was treated with $(Me_3SI)_3SiH$ (0.7 ml, 2.63 mmol). The reaction was warmed at reflux, and three additional equivalents of Tempo (3x410 mg) and $(Me_3SI)_3SiH$ (4x0.7 ml) were added sequentially in four portions over the next 45 minutes. After 12 h (TLC: Et_2O-light petroleum 3 : 7), the reaction was cooled to 25 °C and the solvent removed under reduced pressure. The residue, after crystallization (MeOH), afforded the desired compund as pale yellow solid (yield 98%).

m.p. (Et_2O-light petroleum) 185-186 °C

IR (KBr) cm^{-1}: 1710, 1660, 1635, 1435

^1H NMR ($CDCl_3$) δ: 1.06-1.12 (m, 15H); 1.57-1.59 (m, 12H); 2.55 (s, 3H); 3.83-3.91 (m, 4H); 4.39-4.44 (d, 1H, J=10Hz); 5.27 (s, 2H); 7.04 (s, 1H); 7.31-7.52 (m, 6H).

By analogous procedure the following compound can be prepared:

(±)-4-Benzyloxy-2-methyl-6-(tert-butyloxycarbonyl)-8-[(2',2',6',6'-tetramethylpiperidinyl-N-oxy)methyl]-7,8-dihydro-thieno[2,3-e]indole

m.p. (Et_2O-light petroleum) 160-163 °C

IR (KBr) cm^{-1}: 1710, 1660, 1635, 1435

^1H NMR ($CDCl_3$) δ: 1.11-1.16 (s, 9H); 1.25-1.47 (m, 9H); 1.62 (s, 9H); 2.56 (s, 3H); 3.65-3.67 (m, 1H); 3.79-3.88 (m, 1H); 4.14-4.21 (m, 3H); 5.23 (s, 2H); 7.14 (s, 1H); 7.15-7.71 (m, 6H).

Step -10- The intermediate (±)-8-Benzyloxy-3-methyl-6-(tert-butyloxycarbonyl)-4-(hydroxymethyl)-4,5-dihydro-thieno[3,2-e]indole

A solution of intermediate 8 (1.9 g, 3.37 mmol) in 78 mL of a 3:1:1 mixture of AcOH-THF-H_2O was treated with zinc powder (2.73 g, 41.6 mmol), and the resulting suspension was warmed at 70 °C with vigorous stirring. After 3 h (TLC: Et_2O-light petroleum 7 : 3), the reaction mixture was cooled at 25 °C and the zinc was removed by filtration. The solvent was removed under reduced pressure, and the resulting residue was dissolved in EtOAc (40 ml) and filtered. The solution was concentrated and the residue purified by flash chromatography (Et_2O-light petroleum 7 : 3), to afford the intermediate as a white solid (yield 93%).

m.p. (Et_2O-light petroleum) 84-85°C

IR (KBr) cm^{-1}: 3500, 1710, 1620, 1530

^1H NMR ($CDCl_3$) δ: 1.58 (s, 10H); 2.56 (s, 3H); 3.56 (m, 1H); 3.79-4.03 (m, 3H); 4.22-4.27 (d, 1H, J=10Hz); 5.28 (s, 2H); 7.08 (s, 1H); 7.32-7.52 (m, 6H).

By analogous procedure the following compound can be prepared:

(±)-4-Benzyloxy-2-methyl-6-(tert-butyloxycarbonyl)-8-(hydroxymethyl)-7,8-dihydro-thieno[2,3-e]indole

m.p. (Et_2O-light petroleum) 158-160 °C

IR (KBr) cm^{-1}: 3500, 1710, 1620, 1530

^1H NMR ($CDCl_3$) δ: 1.57 (s, 10H); 2.53 (s, 3H); 3.59-3.66 (m, 1H); 3.9-4.22 (m, 4H); 5.19 (s, 2H); 7.13-7.72 (m, 7H).

Step -11- The intermediate (±)-8-Benzyloxy-3-methyl-6-(tert-butyloxycarbonyl)-4-(chloromethyl)-5,6-dihydro-thieno[3,2-e]indole

A solution of intermediate 9 (500 mg, 1.176 mmol) and Ph_3P (635 mg, 2.35 mmol) in dry DCM(1.1 mL) at 24 °C under argon was treated with freshly distilled CCl_4 (0.7 mL, 7.05 mmol), and the reaction mixture was stirred for 20 hours at 24 °C. Flash chromatography (Et_2O-light petroleum 4:6) afforded the desired intermediate as a white solid (yield 98%).

m.p. (Et_2O-light petroleum) 142-143°C

IR (KBr) cm^{-1}: 3450-3070, 1740, 1610, 1530, 1475

^1H NMR ($CDCl_3$) δ: 1.59 (s, 9H); 2.53 (s, 3H); 3.28-3.38 (m, 1H); 3.66-3.72 (m, 1H); 3.92-4.0 (m, 2H); 4.26 (m, 1H); 5.27 (s, 2H); 7.11 (s, 1H); 7.32-7.51 (m, 6H).

m.p. (Et_2O-light petroleum) 170-172 °C

By analogous procedure the following compound can be prepared:

(±)-4-Benzyloxy-2-methyl-6-(tert-butyloxycarbonyl)-8-(chloromethyl)-7,8-dihydro-thieno[2,3-e]indole

IR (KBr) cm^{-1}: 3400-3150, 1740, 1610, 1530, 1475

^1H NMR ($CDCl_3$) d: 1.58(s, 9H); 2.53 (s, 3H); 3.52-3.62 (m, 2H); 3.76-3.85 (m, 1H); 3.98-4.24 (m, 2H); 5.22 (s, 2H); 7.13 (s, 1H); 7.3-7.5 (m, 6H).

The title compound

A mixture of the intermediate 10 (220 mg, 0.495 mmol), HCO_2NH_4 (204 mg, 3.20 mmol), 10% Pd-C (233 mg) in dry

acetone (18 mL) was warmed at reflux for 1.30 h. The catalyst was removed by filtration and the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc (20 mL) and washed with water (10 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (Et_2O-light petroleum 1:1) afforded the title compound as white solid (yield 95%).

m.p. (Et_2O-light petroleum) 198°C

IR (KBr) cm^{-1}: 1740, 1605, 1520, 1460

EI: m/z 353, (20, $[M]^{+\cdot}$); 297 (40, $[M - (CH_3)_2\text{-}C{=}CH_2]^{+\cdot}$); 248 (100, $[M - (CH_3)_2\text{-}C{=}CH_2 - {\cdot}CH_2Cl]^{+}$); 204 (40, $[M - (CH_3)_2\text{-}C{=}CH_2 - {\cdot}CH_2Cl - CO_2]^{+}$)

^1H NMR ($CDCl_3$) δ: 1.59 (s, 9H); 2.54 (s, 3H); 3.32-3.38 (m, 1H); 3.6-3.73 (m, 1H); 3.93-3.99 (m, 2H); 4.2-4.38 (m, 1H); 6.8 (s, 1H); 7.11 (s, 1H); 7.52 (s, 1H).

By analogous procedure the following compound can be prepared:

(±) 2-methyl-4-hydroxy-6-(tert-butyloxycarbonyl)-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole (comp. 30)

m.p. (Et_2O-light petroleum) 193-195°C

IR (KBr) cm^{-1}: 1735, 1600, 1520, 1465

EI: m/z 353, (20, $[M]^{+\cdot}$); 297 (40, $[M - (CH_3)_2\text{-}C{=}CH_2]^{+\cdot}$); 248 (100, $[M - (CH_3)_2\text{-}C{=}CH_2 - {\cdot}CH_2Cl]^{+}$); 204 (40, $[M - (CH_3)_2\text{-}C{=}CH_2 - {\cdot}CH_2Cl - CO_2]^{+}$)

^1H NMR ($CDCl_3$) δ: 1.58 (s, 9H) ; 2.53 (s, 3H); 3.49-3.3.59 (m, 1H); 3.73-3.80 (m, 1H); 3.97-4.22 (m, 3H); 6.75 (s, 1H); 7.06(s, 1H); 7.52 (s, 1H).

Example 2

(±) 7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one hydrochloride (comp. 1)

Step -1- The intermediate (±) 3-methyl-4-(chloromethyl)-8-hydroxy-4,5-dihydro-thieno[3,2-e]-indole hydrochloride (comp. 27).

A solution of compound 29 (80 mg, 0.22 mmol) in 3M HCl-EtOAc (8 mL) at 0 °C was stirred for 30 minutes before removing the solvent under vacuum. The resulting crude amine was purified by flash chromatography (eluent methylene chloride-ethanol 9:1) yielding the intermediate as a yellow powder (yield 90%)

EI: m/z 252, (30, $[M]^{+\cdot}$)

By analogous procedure the following compound can be prepared:

(±) 2-methyl-4-hydroxy-8-(chloromethyl)-7,8-dihydro-thieno[2,3-e]-indole hydrochloride (comp 28)

EI: m/z 252, (20, $[M]^{+\cdot}$)

Step -2- The title compound

A solution of compound 27 (50mg , 0.17mmol) in THF-DMF (3:1, 10 mL) at 0 °C was treated with NaH (28mg, 60% in oil, 0.69 mmol). The reaction mixture was stirred for 30 min at 0 °C and for 1 hour at room temperature, before the addition of 2N HCl untill pH acid and THF (15 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by flash chromatography (methylene chloride-ethanol 8:2) to afford the title compound as pale yellow solid (yield 70%).

ESI: m/z 218, (30, $[M+H]^+$)

^1H NMR (DMSO) δ: 1.25-1.32 (m, 1H); 1.95 (m, 1H); 2.30 (s, 3H); 3.05-3.15 (m, 1H); 4.10-4.19 (m, 2H); 4.55 (bs, 1H); 7.04 (s, 1H); 12.50 (bs, 1H).

By analogous procedure the following compound can be prepared:

(±) 6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one hydrochloride (comp 2)

ESI: m/z 218, (40, $[M+H]^+$)

^{1}H NMR (DMSO) δ: 1.25-1.32 (m, 1H); 1.92 (m, 1H); 2.30 (s, 3H); 3.05-3.17 (m, 1H); 4.08-4.15 (m, 2H); 4.55 (bs, 1H); 7.10 (s, 1H); 12.55 (bs, 1H)

Example 3

(±) 3-methyl-4-(chloromethyl)-6-(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole (comp 31)

To a solution of compound 27 (example 3 step 1) (80mg, 0.28mmol) in dry DMF (4 mL), 5,6,7-trimethoxy-1H-indol-2-carboxilic acid (74mg, 0.336 mmol) and EDCI (226mg, 0.84mmol) were added. The reaction was stirred for 18 hours at room temperature, water (20 mL) was added to the reaction mixture and the precipitate was filtered off and purified by flash chromatography (CH_2Cl_2-EtOH 9:1) to afford the desired compound as a yellow powder (yield 75%).

m.p. (DMF-water) 275-280 °C (dec)

IR (KBr) cm^{-1}: 1710, 1685, 1610, 1515, 1465, 1400

ESI: m/z 487, (100, $[M+H]^+$); 509, (40, $[M-Na]^+$)

^{1}HNMR (DMSO) δ: 2.08 (s, 3H); 3.49-3.62 (m, 1H); 3.79-3.85 (m, 1H); 3.79 (s, 3H); 3.81 (s, 3H); 3.92 (s, 3H); 4.02-4.18 (m, 1H); 4.22-4.45 (m, 1H); 4.49-4.60 (m, 1H); 6.96 (s, 1H); 7.01 (s, 1H); 7.41 (s, 1H); 7.77 (bs, 1H); 10.52 (s, 1H); 11.22 (s, 1H).

By analogous procedure and using the opportune intermediate the following compounds can be prepared:

(±) 2-methyl-4-hydroxy-6-(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole (comp 32);

m.p. (DMF-water) 280-282 °C (dec)

IR (KBr) cm^{-1}: 1710, 1685, 1605, 1510, 1450, 1400

ESI: m/z 487, (90, $[M+H]^+$); 509, (70, $[M+Na]^+$)

^{1}HNMR (DMSO) δ: 2.52 (s, 3H); 3.79 (s, 3H); 3.81 (s, 3H); 3.92 (s, 3H); 3.94-4.01 (m, 3H); 4.30-4.40 (m, 1H); 4.61-4.73 (m, 1H); 6.95 (s, 1H); 7.01 (s, 1H); 7.12 (s, 1H); 7.74 (bs, 1H); 10.02 (s, 1H); 11.38 (s, 1H);

(±) 3-methyl-4-(chloromethyl)-6-[[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole (comp 33);

m.p. (DMF-water) > 300 °C (dec)

IR (KBr) cm^{-1}: 3050, 1710, 1690, 1600, 1520, 1460, 1400

ESI: m/z 555, (100, $[M+H]^+$)

^{1}HNMR (DMSO) δ: 2.54 (s, 3H); 3.56-3.62 (m, 1H); 388-3.92 (m, 1H); 4.14-4.21 (m, 1H); 4.56-4.75 (m, 2H); 6.90-7.20 (m, 3H); 7.25-7.61 (m, 6H); 7.80 (s, 1H); 8.23 (d, 1H, J=2Hz); 10.19 (s, 1H); 10.56 (s, 1H); 11.75 (s, 2H);

(±) 2-methyl-4-hydroxy-6-[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole (comp 34);

m.p. (DMF-water) > 300 °C

IR (KBr) cm^{-1}: 3100-300, 1700, 1680, 1615, 1520, 1445, 1400

ESI: m/z 555, (100, $[M+H]^+$)

^{1}HNMR (DMSO) δ: 2.53 (s, 3H); 3.85-4.12 (m, 3H); 4.38-4.51 (m, 1H); 4.65-4.87 (m, 1H); 7.03-7.25 (m, 3H); 7.43-7.66 (m, 6H); 7.84 (s, 1H); 8.23 (s, 1H); 10.10 (s, 1H); 10.18 (s, 1H); 11.74 (s, 2H);

(±) 3-methyl-4-(chloromethyl)-6-[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole (comp 35);

m.p. (DMF-water) 210-212 °C

IR (KBr) cm^{-1}: 3045, 1715, 1695, 1600, 1515, 1450, 1400

ESI: m/z 556, (100, $[M+H]^+$)

^{1}HNMR (DMSO) δ: 2.54 (s, 3H); 3.56-3.66 (m, 1H); 3.88-3.93 (m, 1H); 4.14-4.21 (m, 1H); 4.56-4.69 (m, 2H); 7.20 (s, 1H); 7.33-7.63 (m, 5H); 7.72-7.85 (m, 4H); 8.22 (s, 1H); 10.50 (s, 1H); 10.56 (s, 1H); 11.77 (s, 1H);

(±) 2-methyl-4-hydroxy-6-[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole (comp 36);
m.p. (DMF-water) 280-282 °C (dec)
IR (KBr) cm^{-1}: 3060; 1700, 1675, 1610, 1515, 1440, 1400
ESI: m/z 556, (100, $[M+H]^+$)
^{1}HNMR (DMSO) δ: 2.53 (s, 3H); 3.91-4.11 (m, 3H); 4.42-4.55 (m, 1H); 4.72-4.89 (m, 1H); 7.14-7.20 (m, 2H); 7.33-7.63 (m, 4H); 7.77-7.84 (m, 4H); 8.22 (s, 1H); 10.10 (s, 1H); 10.50 (s, 1H); 11.75 (s, 1H);
(±) 3-methyl-4-(chloromethyl)-6-(5-amino-1H-indol-2-ylcarbonyl)-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole (comp 37);
(±) 2-methyl-4-hydroxy-6-(5-amino-1H-indol-2-ylcarbonyl)-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole (comp 38);
(±) 3-methyl-4-(chloromethyl)-6-(5-amino-1H-benzofuran-2-ylcarbonyl)-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole (comp 39);
(±) 2-methyl-4-hydroxy-6-(5-amino-1H-benzofuran-2-ylcarbonyl)-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole (comp 40);
(±) 3-methyl-4-(chloromethyl)-6-[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole (comp 41);
(±) 2-methyl-4-hydroxy-6-[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole (comp 42);
(±) 3-methyl-4-(chloromethyl)-6-[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole (comp 43);
(±) 2-methyl-4-hydroxy-6-[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole (comp 44);
(±) 3-methyl-4-(chloromethyl)-6-[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole (comp 45);

(±) 2-methyl-4-hydroxy-6-[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole (comp 46);

(±) 3-methyl-4-(chloromethyl)-6-[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole (comp 47);

(±) 2-methyl-4-hydroxy-6-[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole (comp 48);

(±) 3-methyl-4-(chloromethyl)-6-[5-[[5-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole (comp 49);

(±) 2-methyl-4-hydroxy-6-[5-[[5-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole (comp 50);

(±) 3-methyl-4-(chloromethyl)-6-[5-[[5-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole (comp 51);

(±) 2-methyl-4-hydroxy-6-[5-[[5-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole (comp 52).

Example 4

(±)-2-(tert-butyloxycarbonyl)-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one (comp. 3)

A solution of compound 29 (70 mg, 0.197 mmol) in THF-DMF (3:1, 10 mL) at 0 °C was treated with NaH (24mg, 60% in oil, 0.591 mmol). The reaction mixture was stirred for 30 min at 0 °C and for 1 hour at room temperature, before the addition of pH 7 pnosphate buffer (0.2 M, 20 mL) and THF (15 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by flash chromatography (Et_2O-light petroleum 8:2) to afford the title compound as pale yellow solids (yield 89%).

m.p. (Et_2O-etere di petrolio) 139°C

IR (KBr) cm^{-1}: 1720, 1620, 1590

ESI: m/z 318, (40, $[M+H]^+$); 262 (100, $[M + H - (CH_3)_2-C=CH_2]^{+\cdot}$); 218 (50, $[M - (CH_3)_2-C=CH_2 - {}^{\cdot}CO_2 + H]^+$)

^1H NMR ($CDCl_3$) δ: 1.26-1.29 (m, 2H); 1.49-1.58 (s, 9H); 2.53 (s, 3H); 3.68-4.05 (m, 3H); 7.04 (s, 1H); 7.63 (s, 1H).

By analogous procedure the following compound can be prepared:

(±)2-(tert-butyloxycarbonyl)-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one (comp. 4);

m.p. (Et_2O-light petroleum) 116-118 °C (dec.)

IR (KBr) cm^{-1}: 1720, 1620, 1590

EI: m/z 317, (30, $[M]^{+\cdot}$); 261 (20, $[M - (CH_3)_2-C=CH_2]^{+\cdot}$)

^1H NMR ($CDCl_3$) δ: 1.58 (s, 9H); 1.63-169 (m, 2H); 2.47 (s, 3H); 2.6-2.75 (m, 1H); 3.98 (m, 2H); 6.66 (s, 1H); 7.15(s, 1H);

(±) 2-(5-amino-1H-indol-2-ylcarbonyl)-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one (comp 5);

(±) 2-(5-amino-1H-indol-2-ylcarbonyl)-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one (comp 6);

(±) 2-(5-amino-1H-benzofuran-2-ylcarbonyl)-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one (comp 7);

(±) 2-(5-amino-1H-benzofuran-2-ylcarbonyl)-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one (comp 8);

(±) 2-(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one (comp 9);

(±) 2-(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one (comp 10);

(±) 2-[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one (comp 11);

(±) 2-[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one (comp 12);

(±) 2-[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one (comp 13);

(±) 2-[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one (comp 14);

(±) 2-[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one hydrochloride (comp 15);

(±) 2-[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one hydrochloride (comp 16);

(±) 2-[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one hydrochloride (comp 17);

(±) 2-[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one hydrochloride (comp 18);

(±) 2-[5-[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one (comp 19);

(±) 2-[5-[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one (comp 20);

(±) 2-[5-[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one (comp 21);

(±) 2-[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one (comp 22);

(±) 2-[5-[[5-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one (comp 23);

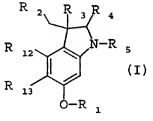
(±) 2-[5-[[5-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one (comp 24);

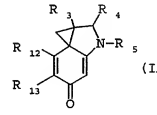
(±) 2-[5-[[5-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one (comp 25);

(±) 2-[5-[[5-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one (comp 26).

CLAIMS

1. A compound which is a thieno-indole derivative of formula (I) or (IA)


(I)


(IA)

wherein

R_1 is hydrogen; C_1-C_4 alkyl; $-COR_6$ wherein R_6 is C_1-C_4 alkyl unsubstituted or substituted by phenyl which, in its turn, is unsubstituted or substituted by 1 to 3 substituents independently chosen from C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen and CF_3; or $-CONHR_6$ wherein R_6 is as defined above;

R_2 is halogen;

R_3 and R_4 are, each independently, hydrogen or C_1-C_4 alkyl;

R_5 is hydrogen or a substituent selected from:

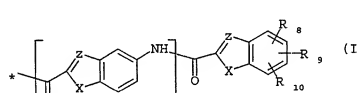
a) COR_7 in which R_7 is i) C_1-C_4 alkoxy or ii) a saturated or unsaturated, straight or branched C_1-C_{18} aliphatic hydrocarbon chain unsubstituted or substituted by one or more substituents independently chosen from hydroxy, C_1-C_4 alkoxy, cyano, $-C(NH)-NH_2$ and $-NR'R''$ in which R' and R", being the same or different, are hydrogen or C_1-C_4 alkyl, or iii) a saturated or unsaturated, straight or branched C_1-C_{12} aliphatic hydrocarbon chain ω-substituted by an aryl or heteroaryl group which, in its turn, is unsubstituted or substituted by 1 to 4 substituents independently chosen from halogen, hydroxy, C_1-C_4 alkoxy, cyano and $-C(NH)-NH_2$;

b) a saturated or unsaturated, straight or branched C_1-C_{18} aliphatic hydrocarbon chain substituted or

unsubstituted by one or more substituents independently chosen from hydroxy, C_1-C_4 alkoxy, cyano, -C(NH)-NH_2 and -NR'R" in which R' and R", being the same or different, are hydrogen or C_1-C_4 alkyl;

c) a saturated or unsaturated, straight or branched C_1-C_{12} aliphatic hydrocarbon chain ω-substituted by an aryl or heteroaryl group which, in its turn, is unsubstituted or substituted by 1 to 4 substituents independently chosen from halogen, hydroxy, C_1-C_4 alkoxy, cyano and -C(NH)-NH_2; and

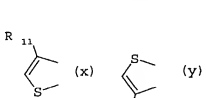
d) a group of formula (III)



(III)

wherein n is 0, 1 or 2; each of Z group is independently -CH= or -N=; each of X group is independently -O-, -S- or -NR- wherein R is hydrogen or C_1-C_4 alkyl; and each of R_3, R_9 and R_{10} is independently hydrogen, halogen, hydroxy, C_1-C_4 alkoxy, cyano, -C(NH)-NH_2 or -NR'R" in which R' and R" are as defined above;

R_{12} and R_{13} taken together form a group (x) or (y):



(x) (y)

in which R_{11} is hydrogen or C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein

R_1 is hydrogen, $-COR_6$ or $-CONHR_6$ wherein R_6 is as defined in claim 1;

R_2 is as defined in claim 1;

R_3 and R_4 are both hydrogen;

R_5 is COR_7 in which R_7 is C_1-C_4 alkoxy, or a group of formula (III) as defined in claim 1; and

R_{12} and R_{13} taken together form a group (x) or (y) as defined in claim 1, in which R_{11} is C_1-C_4 alkyl.

3. A compound according to claim 1 or 2 wherein

R_1 is hydrogen, $-COR_6$ or $-CONHR_6$ wherein R_6 is as defined in claim 1 or 2;

R_2 is as defined in claim 1 or 2;

R_3 and R_4 are both hydrogen;

R_5 is a group of formula (III) as defined in claim 1 or 2 in which Z is -CH=, X is independently -O- or -NH- and each of R_8, R_9 and R_{10} is independently hydrogen, halogen, hydroxy, C_1-C_4 alkoxy, cyano, $-C(NH)-NH_2$ or $-NR'R''$ in which R' and R'' are as defined in claim 1 or 2; and

R_{12} and R_{13} taken together form a group (x) or (y) as defined in claim 1 or 2, in which R_{11} is C_1-C_4 alkyl.

4. A compound selected from the group consisting of

1) (±)7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one;

2) (±)6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one;

3) (±)2-(tert-butyloxycarbonyl)-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one;

4) (±)2-(tert-butyloxycarbonyl)-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one;

5) (±)2-(5-amino-1H-indol-2-ylcarbonyl)-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one;

6) (±)2-(5-amino-1H-indol-2-ylcarbonyl)-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one;

7) (±)2-(5-amino-1H-benzofuran-2-ylcarbonyl)-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one;

8) (±)2-(5-amino-1H-benzofuran-2-ylcarbonyl)-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one;

9) (±)2-(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one;

10) (±)2-(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one;

11) (±)2-[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one;

12) (±)2-[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one;

13) (±)2-[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one;

14) (±)2-[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one;

15) (±)2-[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one hydrochloride;

16) (±)2-[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one hydrochloride;

17) (±)2-[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one hydrochloride;

18) (±)2-[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one hydrochloride;

19) (±)2-[5-[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one;

20) (±)2-[5-[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one;

21) (±)2-[5-[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one;

22) (±)2-[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one;

23) (±)2-[5-[[5-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one;

24) (±)2-[5-[[5-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one;

25) (±)2-[5-[[5-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-7-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[3,2-e]-indol-4-one;

26) (±)2-[5-[[5-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-6-methyl-1,2,8,8a-tetrahydrocyclopropa[c]-thieno-[2,3-e]-indol-4-one;

(27) (±)3-methyl-4-(chloromethyl)-8-hydroxy-4,5-dihydro-thieno[3,2-e]-indole;

28) (±)2-methyl-4-hydroxy-8-(chloromethyl)-7,8-dihydro-thieno[2,3-e]-indole;

29) (±)3-methyl-4-(chloromethyl)-6-(tert-butyloxycarbonyl)-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole;

30) (±)2-methyl-4-hydroxy 6-(tert-butyloxycarbonyl) 8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole;

31) (±)3-methyl-4-(chloromethyl)-6-(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole;

32) (±)2-methyl-4-hydroxy-6-(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole;

33) (±)3-methyl-4-(chloromethyl)-6-[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole;

34) (±)2-methyl-4-hydroxy-6-[5-[(1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole;

35) (±)3-methyl-4-(chloromethyl)-6-[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole;

36) (±)2-methyl-4-hydroxy-6-[5-[(1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole;

37) (±)3-methyl-4-(chloromethyl)-6-(5-amino-1H-indol-2-ylcarbonyl)-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole;

38) (±)2-methyl-4-hydroxy-6-(5-amino-1H-indol-2-ylcarbonyl)-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole;

39) (±)3-methyl-4-(chloromethyl)-6-(5-amino-1H-benzofuran-2-ylcarbonyl)-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole;

40) (±)2-methyl-4-hydroxy-6-(5-amino-1H-benzofuran-2-ylcarbonyl)-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole;

41) (±)3-methyl-4-(chloromethyl)-6-[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole;

42) (±)2-methyl-4-hydroxy-6-[5-[(5-amidino-1H-indol-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole;

43) (±)3-methyl-4-(chloromethyl)-6-[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole;

44) (±)2-methyl-4-hydroxy-6-[5-[(5-amidino-1H-benzofuran-2-ylcarbonyl)-amino]-1H-indol-2-ylcarbonyl]-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole;

45) (±)3-methyl-4-(chloromethyl)-6-[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole;

46) (±)2-methyl-4-hydroxy-6-[5-[[6-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole;

47) (±)3-methyl-4-(chloromethyl)-6-[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole;

48) (±)2-methyl-4-hydroxy-6-[5-[[6-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole;

49) (±)3-methyl-4-(chloromethyl)-6-[5-[[5-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole;

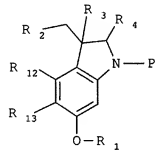
50) (±)2-methyl-4-hydroxy-6-[5-[[5-(N,N-diethylamino)-1H-indol-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole;

51) (±)3-methyl-4-(chloromethyl)-6-[5-[[5-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-8-hydroxy-4,5-dihydro-thieno-[3,2-e]-indole; and

52) (±)2-methyl-4-hydroxy-6-[5-[[5-(N,N-diethylamino)-1H-benzofuran-2-ylcarbonyl]-amino]-1H-indol-2-ylcarbonyl]-8-(chloromethyl)-7,8-dihydro-thieno-[2,3-e]-indole.

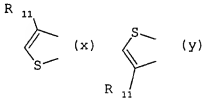
5. A process for preparing a compound of formula (I) or (IA) as defined in claim 1, said process comprising:

A) removing the protecting group in a compound of formula (IV)



(IV)

wherein P is an amino protecting group; R_1 is hydrogen; R_2 is halogen; R_3 and R_4 are, each independently, hydrogen or C_1-C_4 alkyl; R_{12} and R_{13} taken together form a group (x) or (y):



(x) (y)

in which R_{11} is hydrogen or C_1-C_4 alkyl; under acidic conditions, thus obtaining a compound of formula (I) in which R_1 and R_5 are hydrogen and R_2, R_3, R_4, R_{12} and R_{13} are as defined above; or

B) reacting a compound of formula (I), wherein R_5 is hydrogen, R_1, R_2, R_3, R_4, R_{12} and R_{13} are as defined above, with a compound of formula (V)

$$R'_5\text{-}W \qquad (V)$$

wherein R'_5 is as R_5 defined above under a) or d) and W is OH or a good leaving group, thus obtaining a

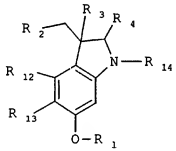
compound of formula (I) wherein R_5 is as defined above under a) or d), respectively; or

C) reacting a compound of formula (I), wherein R_5 is hydrogen and R_1, R_2, R_3, R_4, R_{12} and R_{13} are as defined above, with a compound of formula (VI)

$$R''_5\text{-}W' \qquad \text{(VI)}$$

wherein R''_5 is as R_5 defined above under b) or c) and W' is halogen, thus obtaining a compound of formula (I), wherein R_5 is as defined above under b) or c), respectively; or

D) reacting a compound of formula (VII)



(VII)

wherein R_1 is hydrogen, R_{14} is either an amino protecting group or as R_5 as defined above under a) to d) and R_2, R_3, R_4, R_{12} and R_{13} are as defined above, with a compound of formula (VIII)

$$W'\text{-}C_1\text{-}C_4 \text{ alkyl} \qquad \text{(VIII)}$$

wherein W' is halogen, thus obtaining after removal of the amino protecting group, if present, a compound of formula (I), wherein R_1 is C_1-C_4 alkyl, R_5 is hydrogen or as defined above under a) to d) and R_2, R_3, R_4, R_{12} and R_{13} are as defined above; or

E) reacting a compound of formula (VII) as defined above with a compound of formula (IX)

$$W\text{-}COR_6 \qquad (IX)$$

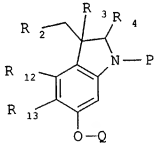
wherein W and R_6 are as defined above, thus obtaining after removal of the amino protecting group, if present, a compound of formula (I) wherein R_1 is $-COR_6$, R_5 is hydrogen or as defined above under a) to d) and R_2, R_3, R_4, R_{12} and R_{13} are as defined above; or

F) reacting a compound of formula (VII) as defined above with a compound of formula (X)

$$R_6\text{-}N{=}CO \qquad (X)$$

wherein R_6 is as defined above, thus obtaining after removal of the amino protecting group, if present, a compound of formula (I) wherein R_1 is $-CONR_6$, R_5 is hydrogen or as defined above under a) to d) and R_2, R_3, R_4, R_{12} and R_{13} are as defined above; or

G) removing the amino and hydroxy protecting groups in a compound of formula (XI)



(XI)

wherein Q is a hydroxy protecting group, P is an amino protecting group and R_2, R_3, R_4, R_{12} and R_{13} are as defined above, thus obtaining a compound of formula (I) wherein R_1 and R_5 are hydrogen; or

H) removing the hydroxy protecting group in a compound of formula (XI) wherein P, being as defined above is -COO-tert-butyl and Q, R_3 and R_4, R_{12} and R_{13} are as defined above, thus obtaining a compound of formula (I) wherein R_1 is hydrogen and R_5, being a COR_7 group as defined above, is -COO-tert-butyl; or

I) reacting a compound of formula (I), in which R_1 is hydrogen and R_2, R_3, R_4, R_5, R_{12} and R_{13} are as defined above, with a basic agent, thus obtaining a compound of formula (IA);

and if desired, converting a compound of the invention into another compound of the invention, and/or, if desired, converting a compound of the invention into a salt thereof, and/or, if desired converting a salt of a compound of the invention into a free compound, and/or, if desired, separating a mixture of isomers of a compound of the invention into the single isomers.

6. A pharmaceutical composition comprising a compound as defined in claim 1, as the active substance, in association with one or more pharmaceutically acceptable excipients and/or carriers.

7. A compound as defined in claim 1 for use in a method of treatment of the human or animal body by therapy.

8. A compound as claimed in claim 7 for use as a cytotoxic agent.

9. A compound as claimed in claim 7 for use as an antineoplastic agent.

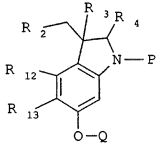
10. A compound as claimed in claim 7, for use in inhibiting the growth of a tumor.

11. A compound as claimed in claim 10 wherein the tumor is a mammary carcinoma, a lung carcinoma, a bladder carcinoma, a colon carcinoma, an ovary or an endometrial tumor, or a sarcoma.

12. A compound as claimed in claim 7 for use in the treatment of hematological malignancies.

13. A compound as claimed in claim 12 in which the hematological malignancy is leukemia.

14. A compound of formula (XI)



(XI)

wherein

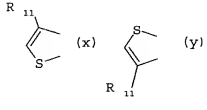
Q is a hydroxy protecting group;

P is an amino protecting group;

R_2 is halogen;

R_3 and R_4 are, each independently, hydrogen or C_1-C_4 alkyl;

and R_{12} and R_{13} taken together form a group (x) or (y):



in which R_{11} is hydrogen or C_1-C_4 alkyl.

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Application No:	GB 9827729.6	**Examiner:**	Peter Davey
Claims searched:	1-14	**Date of search:**	20 January 2000

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.R): C2C (CTY, CWC)

Int Cl (Ed.7): C07D

Other: Online: CAS ONLINE

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
	NONE	

X	Document indicating lack of **novelty or inventive step**	A	**Document indicating technological** background and/or state of the art.
Y	Document indicating lack of **inventive step if combined with** one or more other documents of **same category.**	P	**Document published on** or after the declared priority date but before the **filing date of this invention.**
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